

# FREE RADICALS

**By Doctoral Students**

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# **FREE RADICALS**

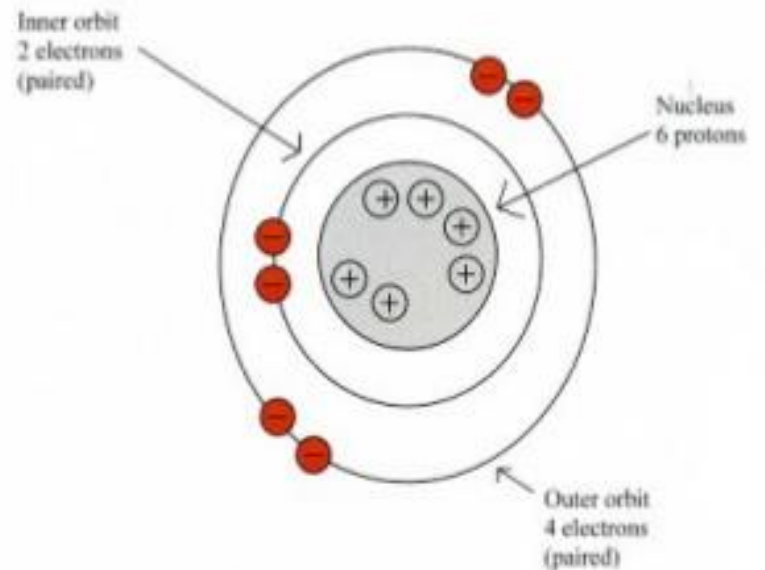
- **INTRODUCTION OF FREE RADICALS**
- **FORMATION OF FREE RADICALS**
- **STABILIZATION OF FREE RADICALS**
- **REACTION OF FREE RADICALS**

# Free radicals

- Radicals are atoms, molecules, or ions with unpaired electrons in outer shell configuration.
- Free radicals may have positive, negative or zero charge.
  - Even though have unpaired electrons, by convention, metals and their ions or complexes with unpaired electrons are not radicals.
- Unpaired electrons cause radicals to be highly reactive.

# Introduction

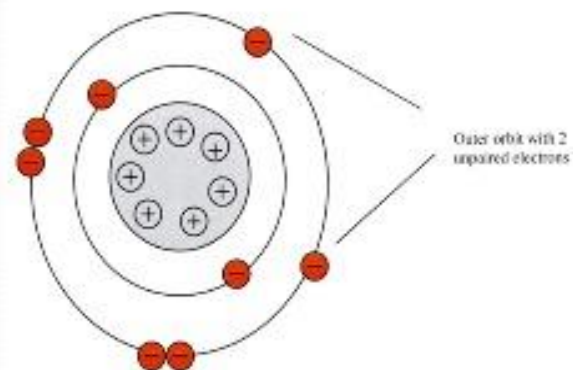
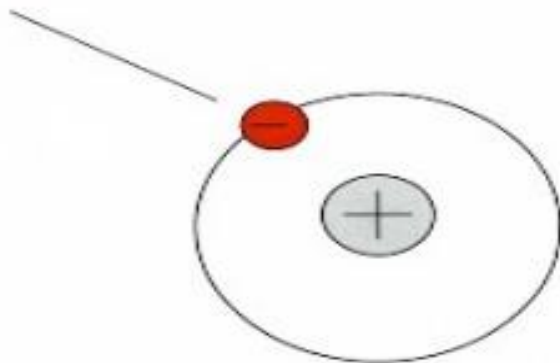
Electron pairing in the outermost orbit indicates stability of the atom. To maintain stability, each electron in the outer orbit must be paired with another electron.

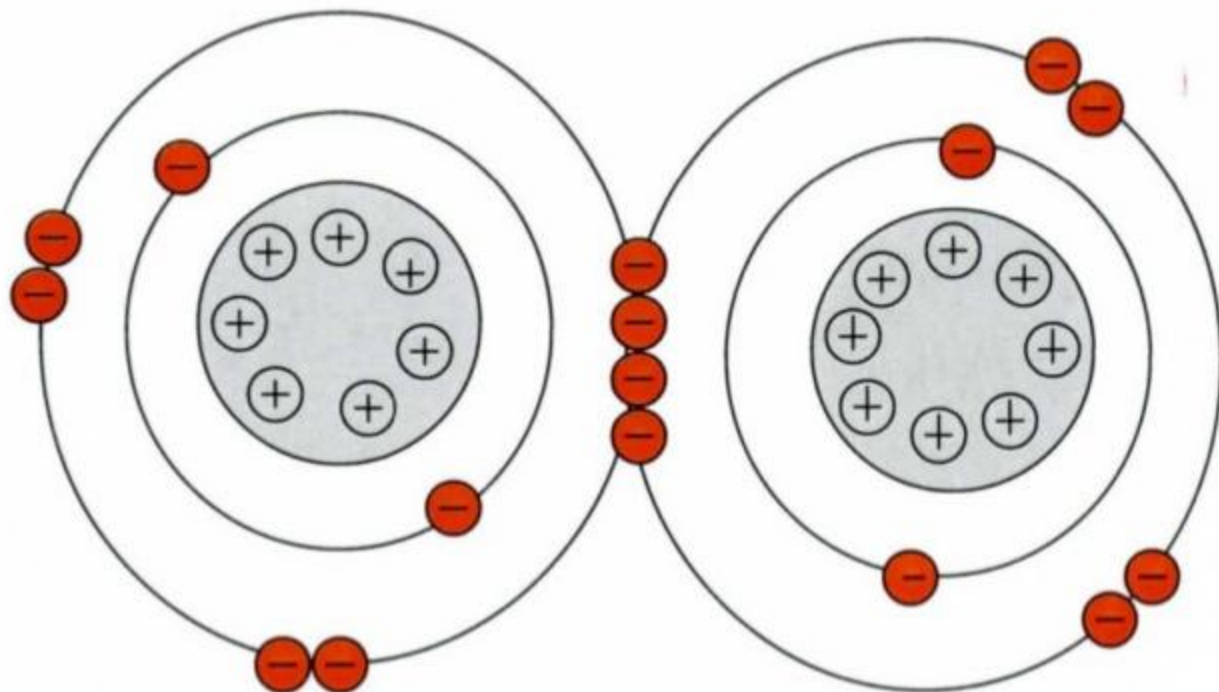


# Introduction

**A free radical is simply an atom with one or more unpaired electrons in its outer orbit.**

Outer orbit with  
A single electron, unpaired





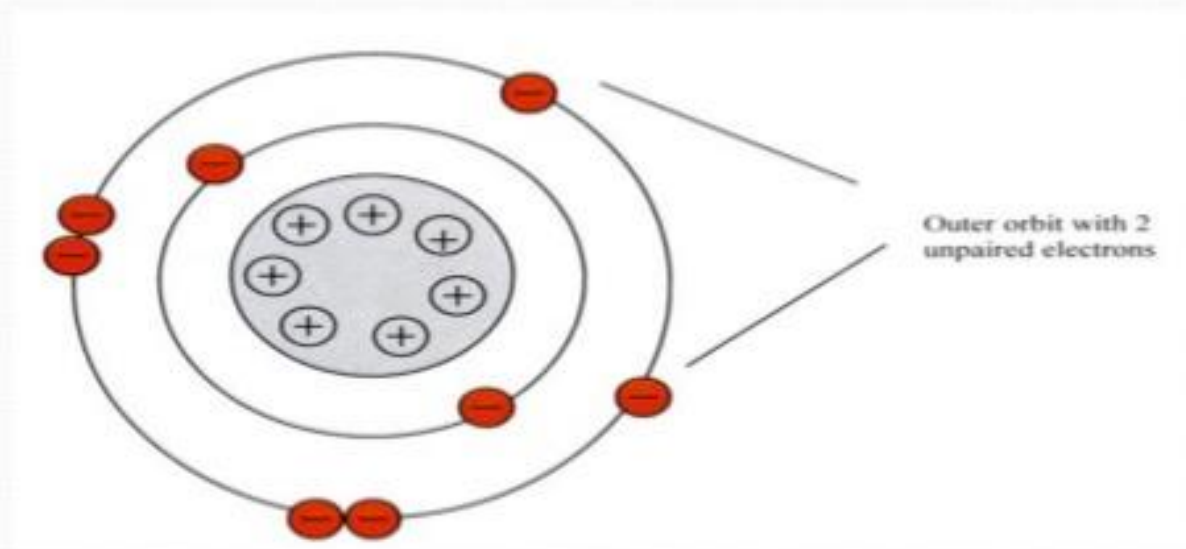


# What happens when free radicals bond?

- When a weak bond is split, a free radical may be formed.
- In normal circumstances, the body provides endogenous substances (free-radical scavengers) to combine with the free radicals. If these scavengers aren't available or if overproduction of free radicals, the radicals donate to or steal an electron from another molecule, leading to a chain reaction that triggers formation of more free radicals. The chain reaction results in damage to the cell membrane and deoxyribonucleic acid (DNA), altered enzyme reactions, and damage to collagen and connective tissues.

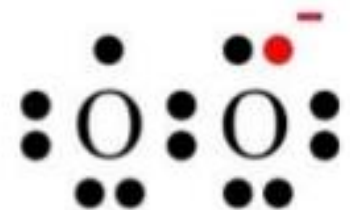
# Oxygen as a free radical

- Probably the most well-known free radical, oxygen is the basis for development of most free radicals in the body. Inherently, oxygen is an unstable molecule.






- During metabolism, the  $O_2$  molecule splits and energy is released. To regain stability, the free single oxygen atom (oxygen free radical) seeks out or steals electrons from other available sources. This may result in a bond with dangerous properties:
- If oxygen accepts one electron, it becomes *superoxide anion radical*.
- If oxygen accepts two electrons, it produces *peroxide*.



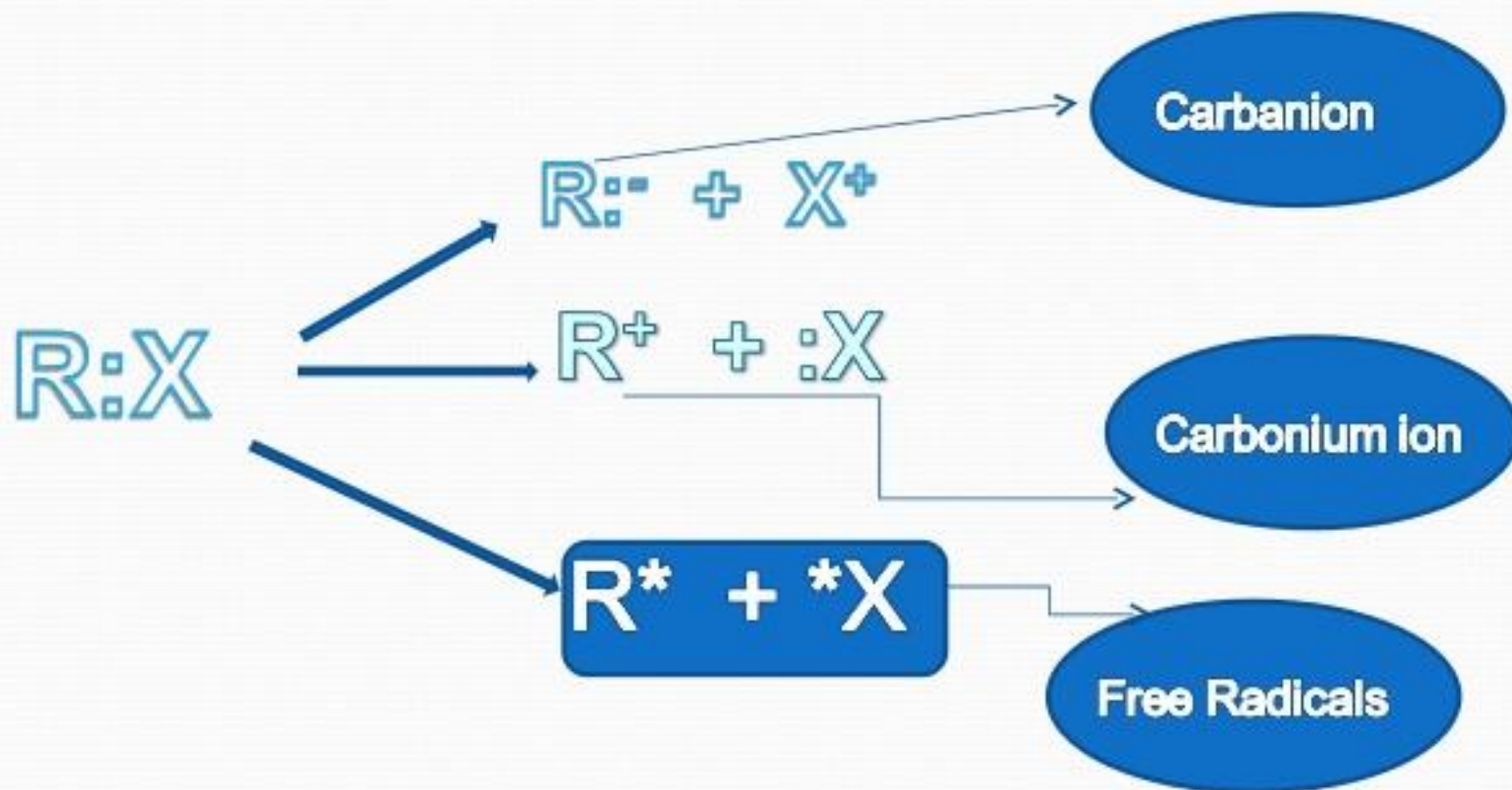
- Although the superoxide radical isn't very powerful, it can easily donate an electron to a nearby iron atom to produce the hydroxyl radical ( $\text{OH}^*$ ), one of the most potent biological free radicals.  $\text{OH}^*$  can react with almost any molecule to cause oxidative stress and damage. These oxygen free radicals also are called reactive oxygen species (ROS).

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- Radicals are believed to be involved in degenerative diseases and cancers.
  - Free radicals play an important role in combustion, atmospheric chemistry, polymerization, plasma chemistry, biochemistry, and many other chemical processes, including human physiology.
    - For example, superoxide and nitric oxide regulate many biological processes including controlling vascular tone.



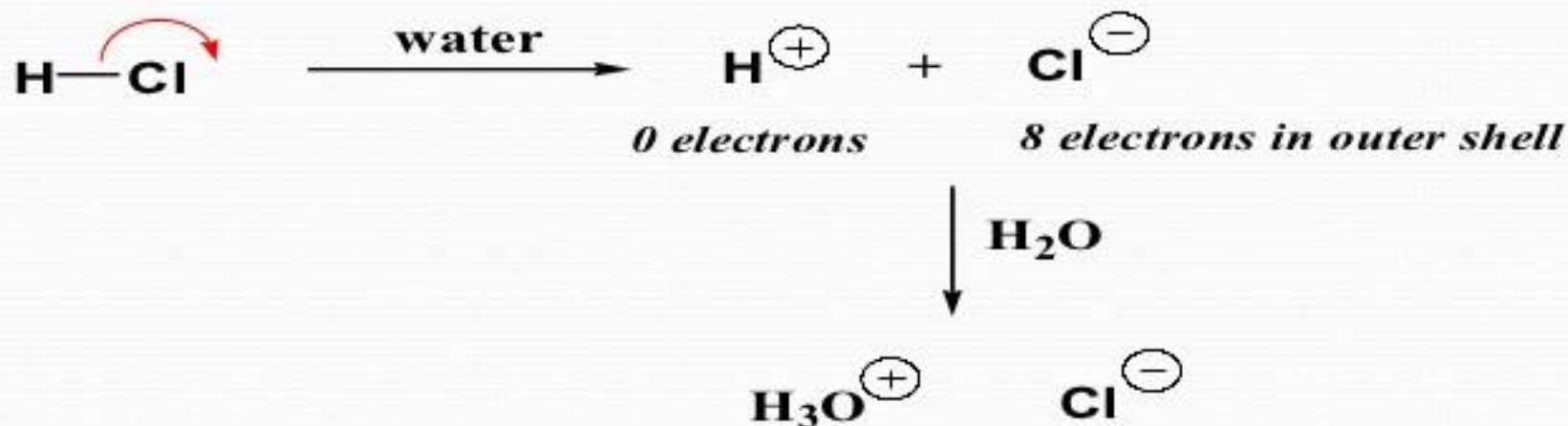
# Fission: Introduction

- Covalent bond can be broken down into 2 ways
- If a covalent compound,  $R:X$ , is broken down, then there are 3 possibilities, which are given as:

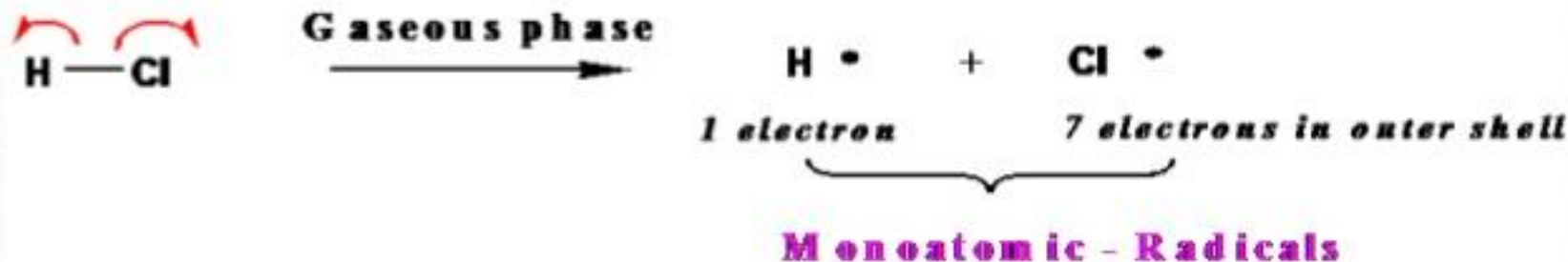


# Heterolytic Fission

ONLY POSSIBLE IN SOLUTION



# Homolytic Fission





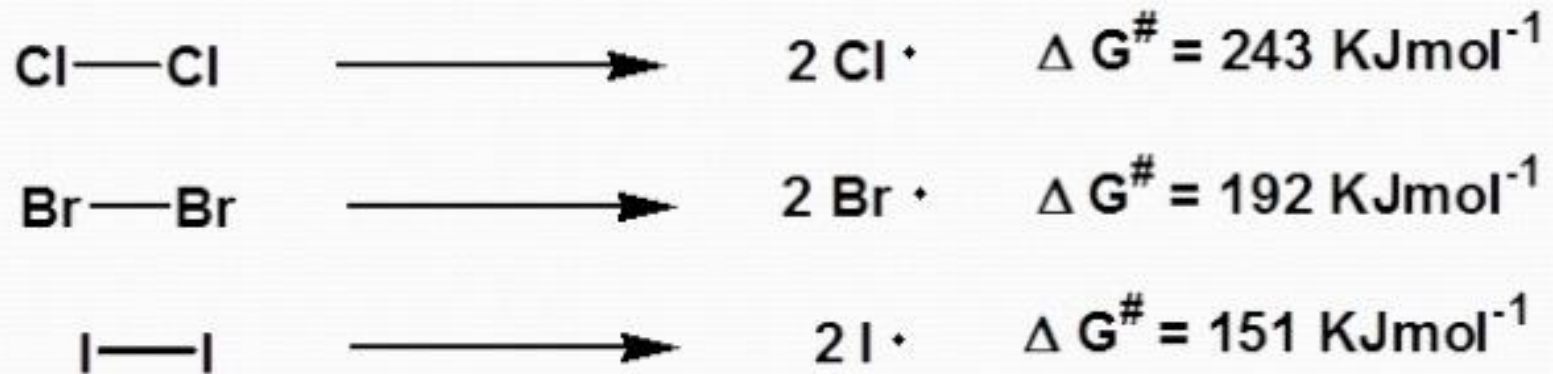
# Radical Formation or Initiation

## Thermolysis or Photolysis

- Light is a good energy source
- Red Light –  $167 \text{ KJmol}^{-1}$
- Blue Light –  $293 \text{ KJmol}^{-1}$
- UV- Light (200 nm) –  $586 \text{ KJmol}^{-1}$

UV light will therefore decompose many organic compounds

## Different molecules require different energy to split



Explains the instability of many iodo-compounds

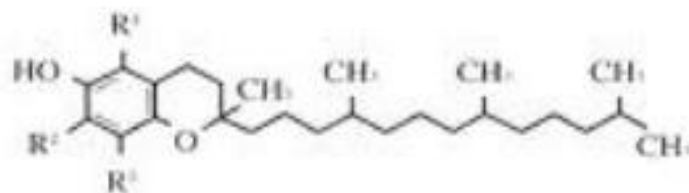
# Important points

- Free radical reactions occur widely in gaseous phase but may also occur in non-polar solvents
- Radicals once formed, produce chain reactions, hence free radical reaction process consists of incitation, propagation and termination
- Produced largely as reaction intermediates
- Most of the radical are short lived but some have long life

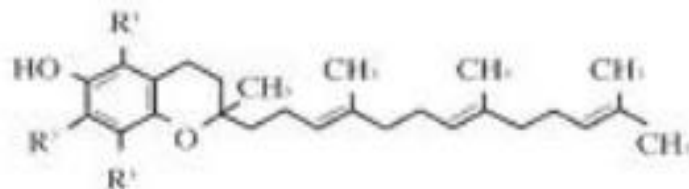
- Stable radicals

The prime example of a stable radical is molecular oxygen  $O_2$ . Organic radicals can be long lived if they occur in a conjugated  $\pi$  system for example vitamin-E

**Vitamin E is a Family of Compounds**



(A)  $\alpha$ -tocopherol ( $R^1 = R^2 = R^3 = \text{CH}_3$ )



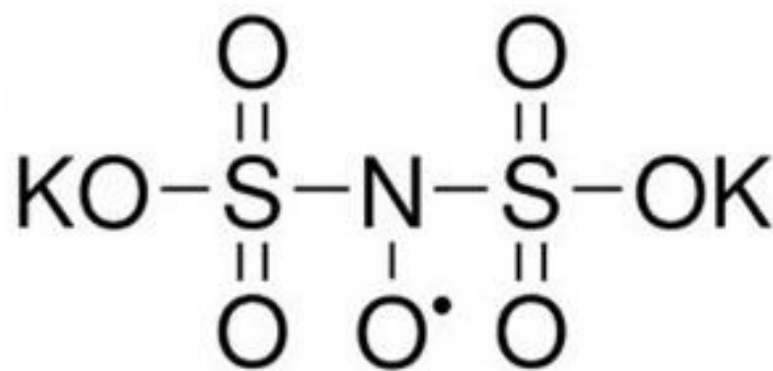
(B)  $\alpha$ -tocotrienol ( $R^1 = R^2 = R^3 = \text{CH}_3$ )

Tocotrienols are part of the vitamin E family.  $\alpha$ -tocopherol (A) and  $\alpha$ -tocotrienol (B) are identical except for the three double bonds (unsaturated) in the long hydrocarbon chain attached to the chromanol ring structure on the left.



# Persistent radicals

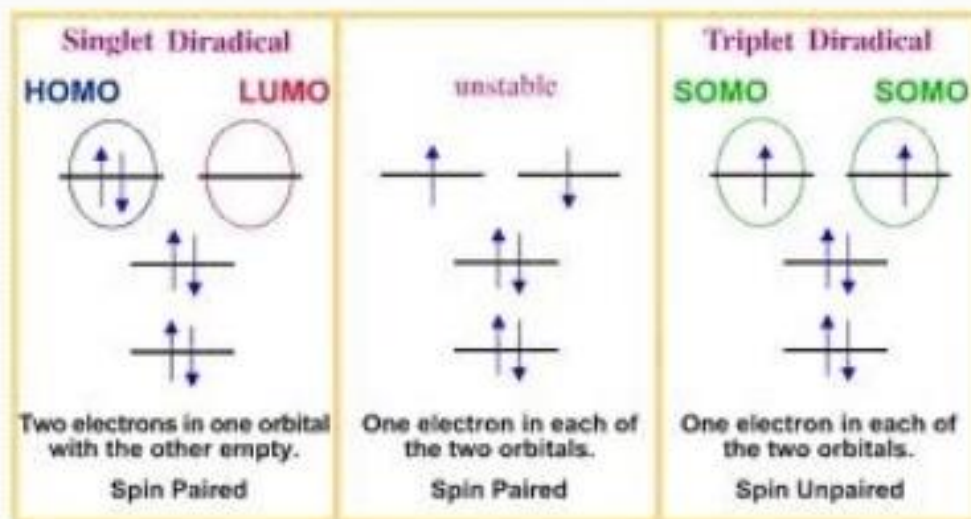
- Persistent radical compounds are those whose longevity is due to steric crowding around the radical centre, which makes physically difficult for the radical to react with another molecule. Examples are Potassium nitroso disulfonate ( $(\text{KSO}_3)_2\text{NO}\cdot$ ) and nitroxides ( $\text{R}_2\text{NO}\cdot$ ).





# Diradicals

- Diradicals are molecules containing two radical centres. Atmospheric oxygen naturally exists as a diradical in its ground state as a triplet oxygen. This state of oxygen results in its paramagnetic character, which is demonstrated by its attraction to an external magnet.



# Short lived radicals (R\*)

- Are difficult to handle, most important and are highly reactive
- Their stability will be in the order:  
 $R_3C^* > R_2CH^* > RCH_2^* > CH_3^*$
- The sequence shows that stability increases due to increase in hyper-conjugation and decrease due to relief of steric strain as the series traversed
- Radical forms having allylic or benzylic are more stable through delocalization of pi electrons e.g



- **Degeneracy** =  $2S+1$ , where **S** is the total electron spin angular momentum.
- An electron has a spin of  $+1/2$  or  $-1/2$ , and an orbital can contain up to two electrons but they must be of opposite spin: the Pauli exclusion principle.

- Singlet diradicals have a pair of electrons, one spin-up and one spin-down [ $+1/2$  and  $-1/2$ ], in one orbital with the second, equal energy orbital, empty.
- The two electron spins are  $+1/2$  and  $-1/2$
- Total electron spin angular momentum,  $S = 0$
- Degeneracy =  $(2^{*}0) + 1 = 0+1 = 1 = \text{singlet}$



- Triplet diradicals have two "spin-up" electrons in adjacent, degenerate (equal energy) orbitals.
- Two electrons of the same spin,  $+1/2$  and  $+1/2$
- Total electron spin angular momentum,  $S = 1$
- Degeneracy =  $(2 \times 1) + 1 = 2 + 1 = 3 = \text{triplet}$

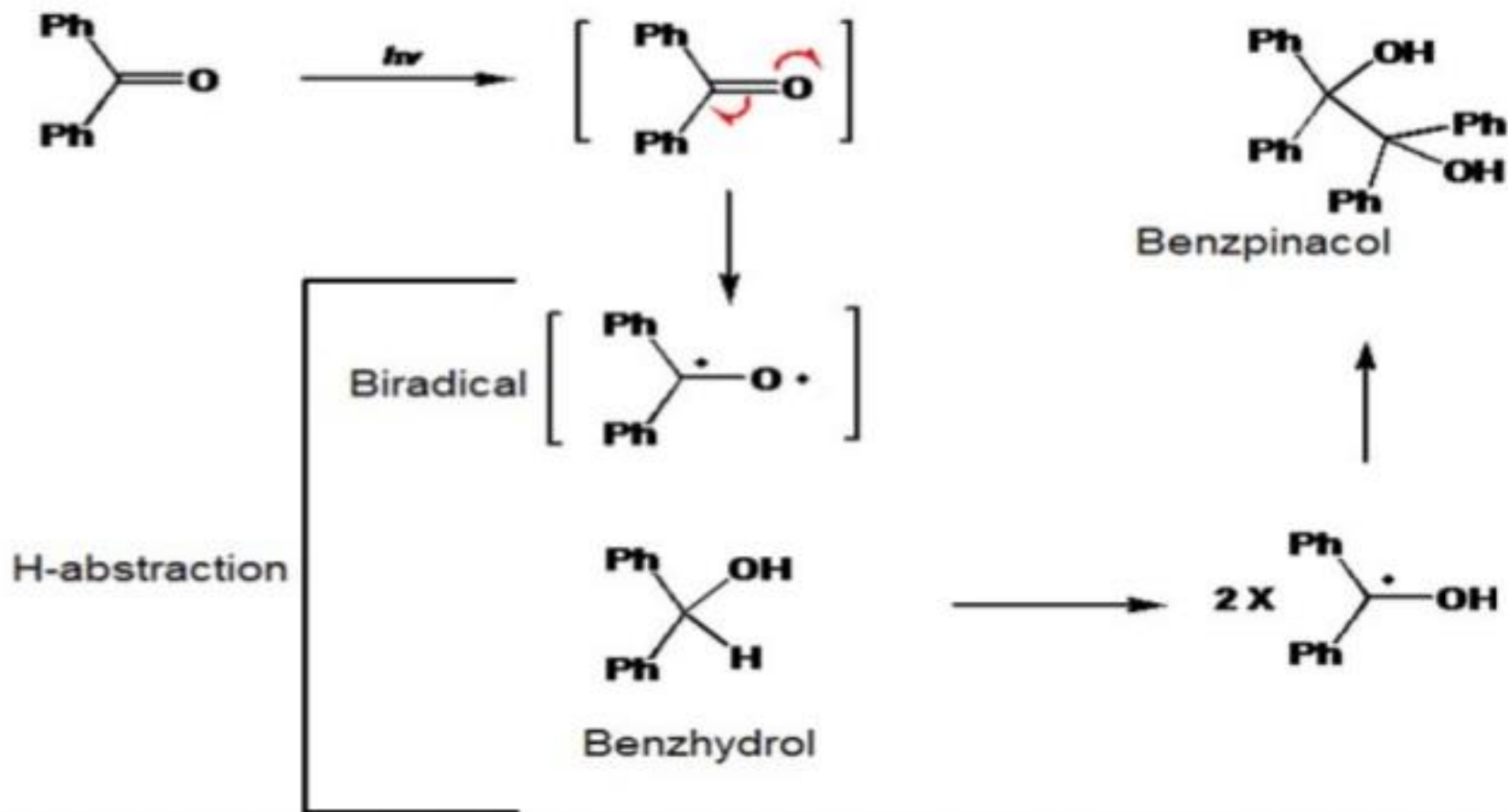


# Methods of preparation

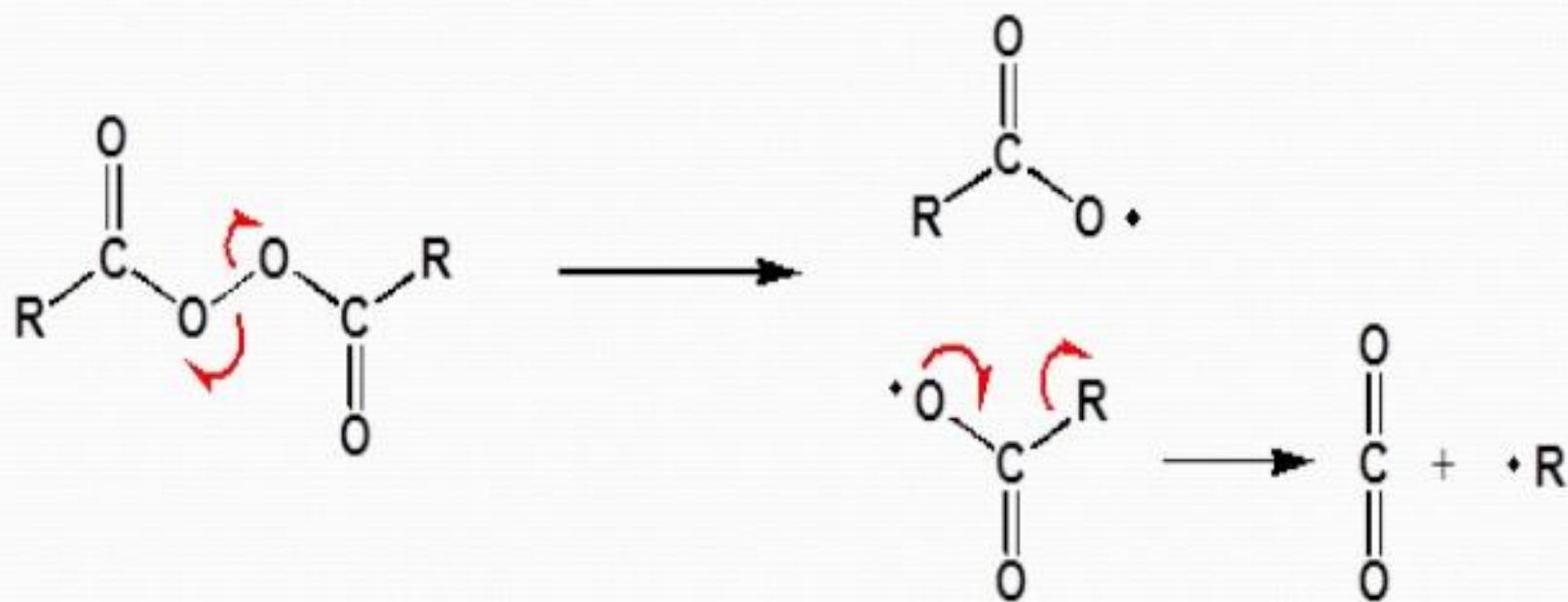
- Photochemical reactions
- Thermal fission
- Oxidation reduction reactions

# Photochemical Reaction

## Diphenylketone



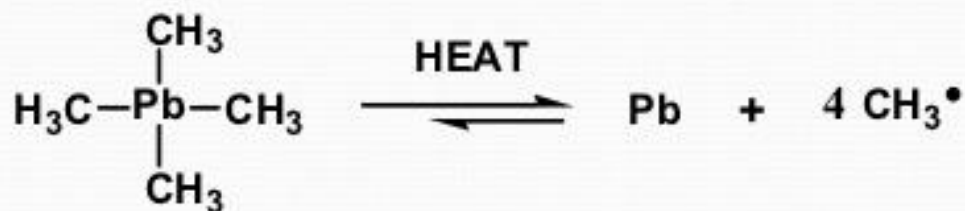
# Peroxides



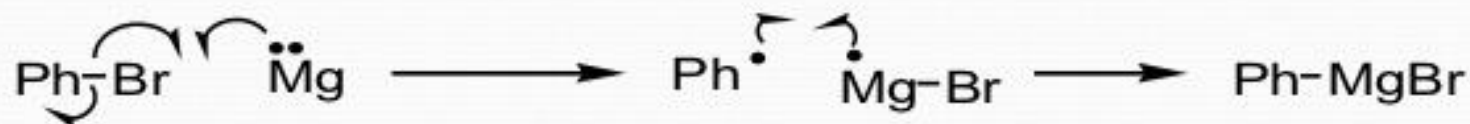
**When R is alkyl, loss of  $CO_2$  is very fast. Therefore, alkyl peroxides are generally avoided, as they tend to be explosive**

## Thermal (OrganoMetallic initiators)

C-M bonds have low Bond Dissociation Energy, and are easily homolyzed into radicals

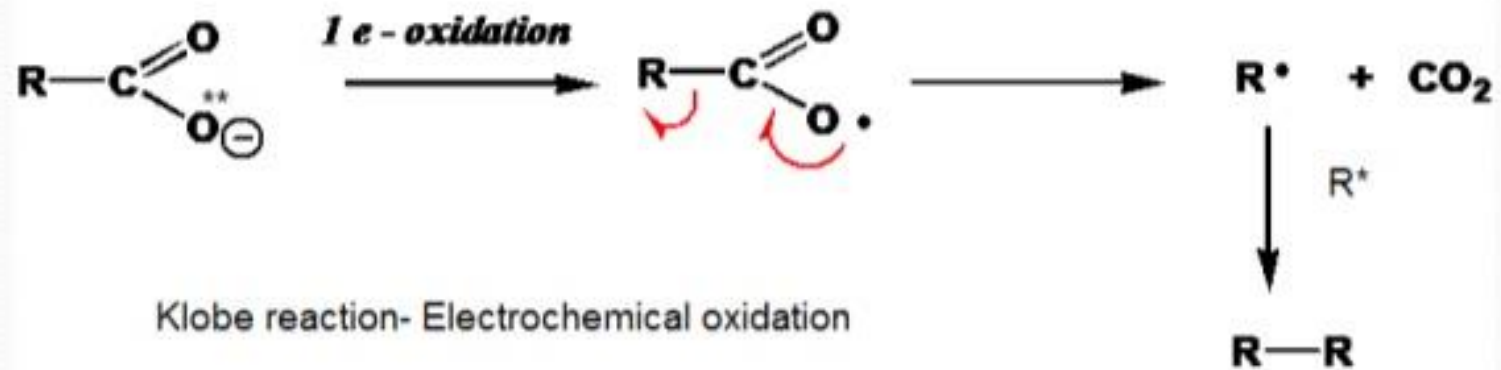


## FORMATION OF GRIGNARD REAGENT

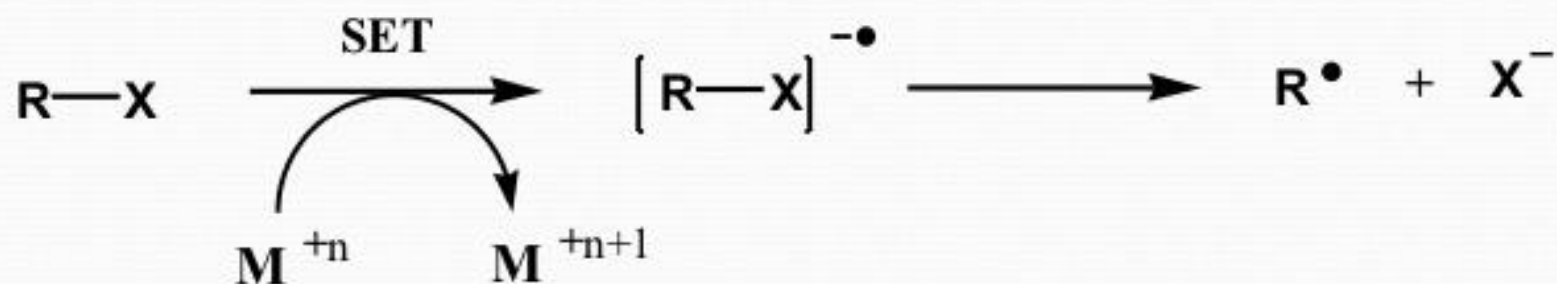


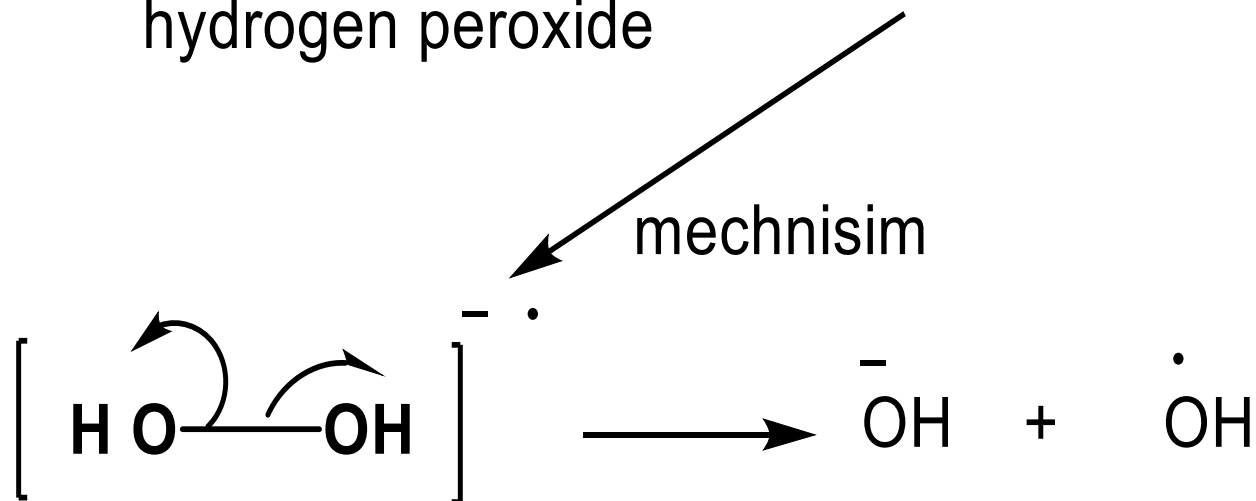
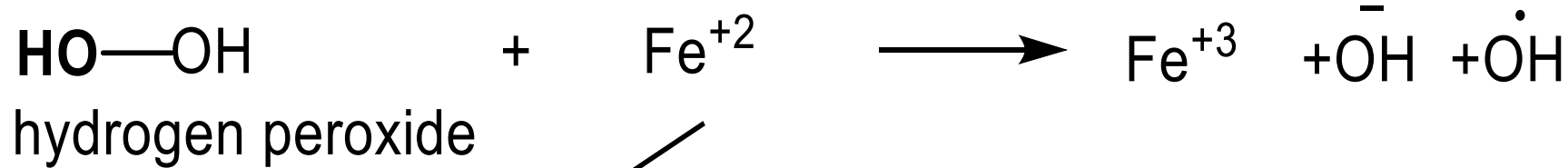


# Oxidation reduction (Electron Transfer Processes)

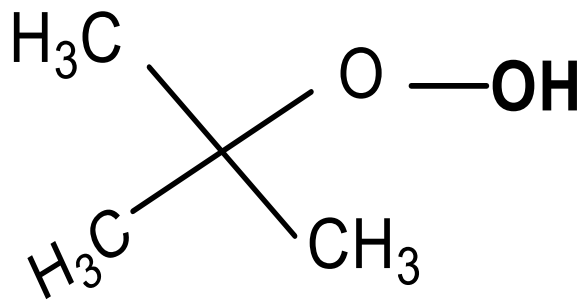
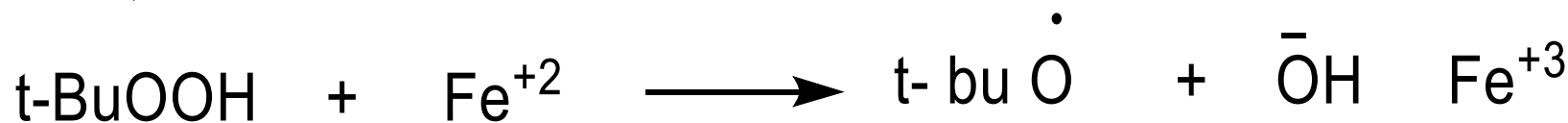


# Single Electron Transfer reactions





also,



Tertiary butylhydroperoxide

# Radical Stability

- 1- Thermodynamic stability
- 2- Kinetic stability



# 1- Thermodynamic Stability

- To break a bond energy is needed, so the energy required to dissociate a bond is a good measure of how strong the bond is

It is quantified in terms of the enthalpy of dissociation of R-H into R• and H•





Q?

- In which case do you think the product is more stable?

A- When bond dissociation energy is high

OR

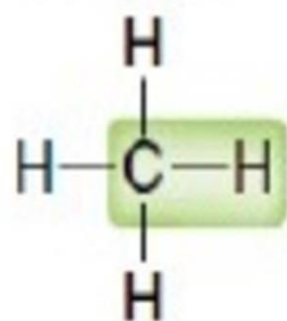
B- When bond dissociation energy is low

# Answer

- The radicals formed from a bond which needs more energy are less stable
  - Electron donating or electron pushing species towards free radicals stabilize them
  - Methane 105 KCal
  - Ethane 101 KCal
  - Isopropane 99 KCal
  - Trimethyl methane 97 KCal
- Tertiary > Secondary > primary > methyl

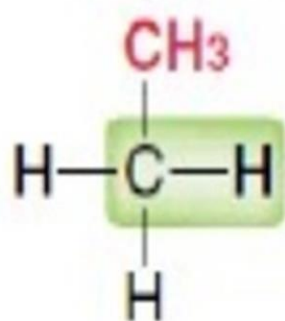
Decreasing BDE

105  
kcal/mol



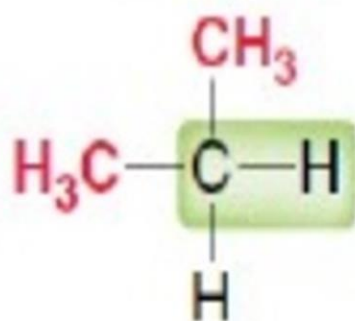
Methyl

101  
kcal/mol



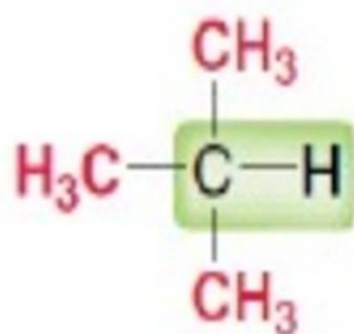
Primary

99  
kcal/mol



Secondary

97  
kcal/mol



Tertiary



# **Factors affecting stability**

**The main factors which determine thermodynamic stability are**

**1- Conjugation**

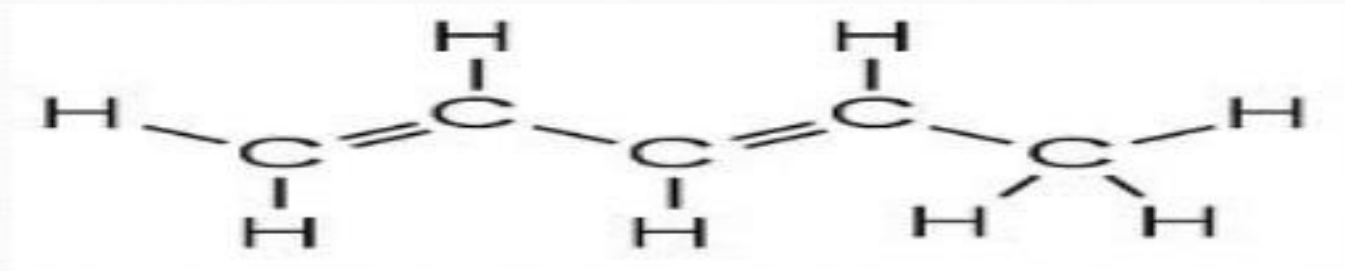
**2- Hybridisation**

**3- Hyperconjugation**

**4-Captodative effects**

# Conjugated system

- It is a system of connected p-orbitals with delocalized electrons in compounds with alternating single and multiple bonds, which in general may lower the overall energy of the molecule and increase stability



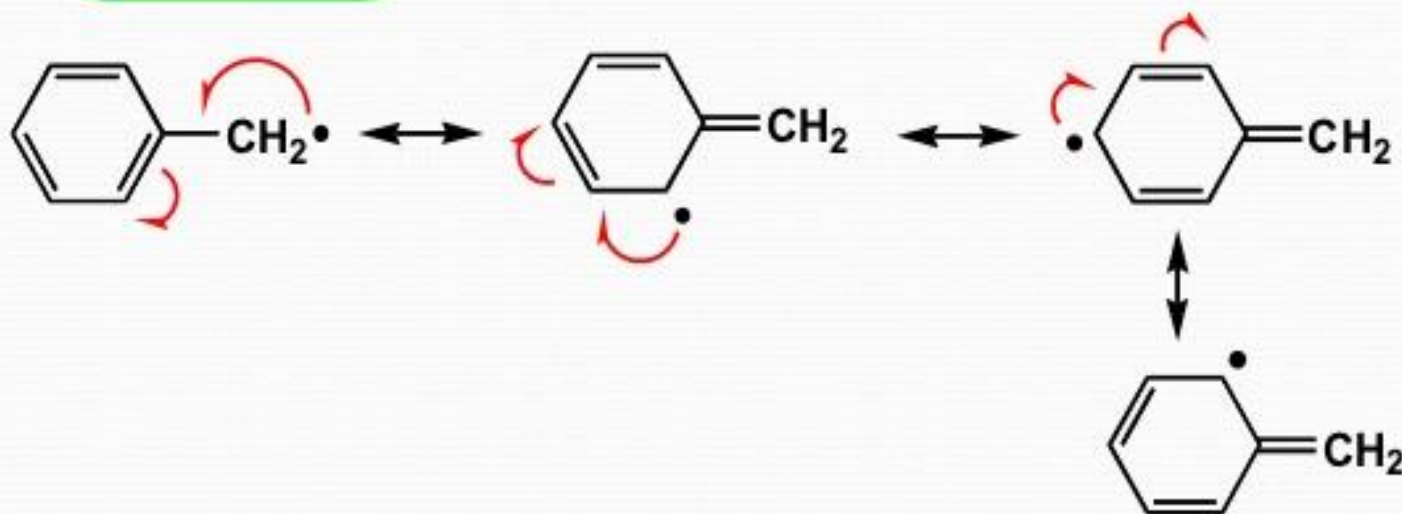
# 1. Conjugation or Mesomerism

This is the primary reason for the existence of stable radicals

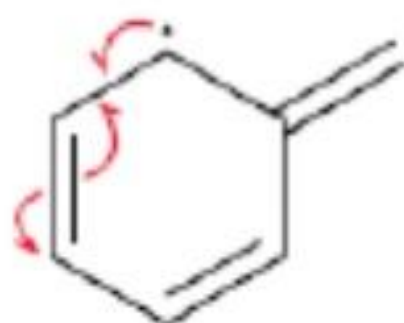
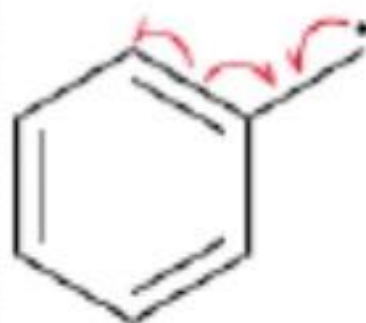
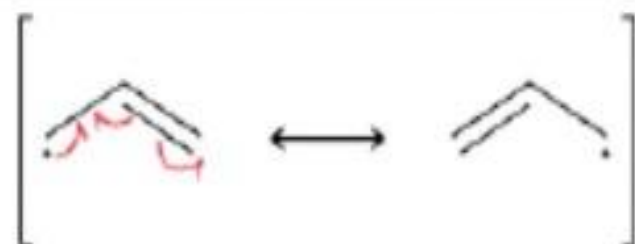
allylic radical



benzylic radical



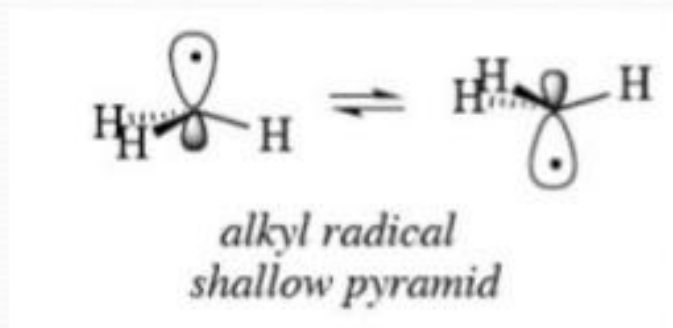
Allylic  
position





# Hybridization

- Geometry of alkyl radical is considered between  $sp^2$  and  $sp^3$  hybridization, and energy required to invert pyramid is very small

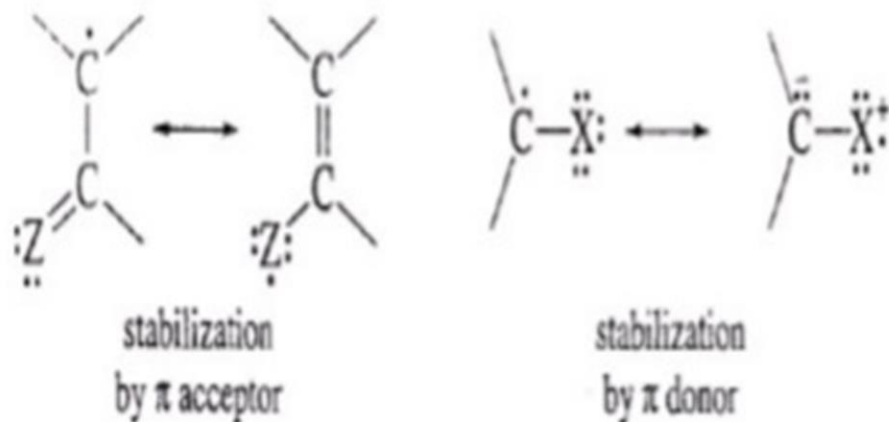


- One can usually think of alkyl radical as if it is  $sp^2$  hybridized. Both electron donating and pi bond stabilize these

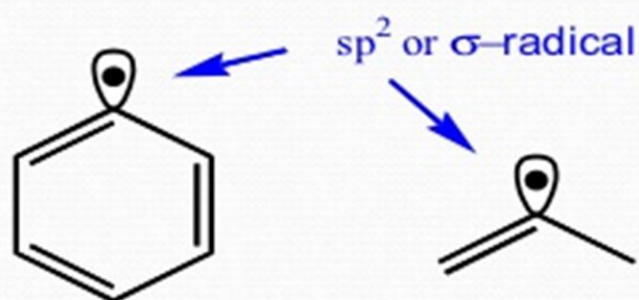
## Hybridisation

**$\pi$ -Radical is more stable than  $\sigma$ -Radical.**

As the  $\pi$ - character of a radical increases, its thermodynamic stabilisation increases



### Vinyl and Aryl Radicals

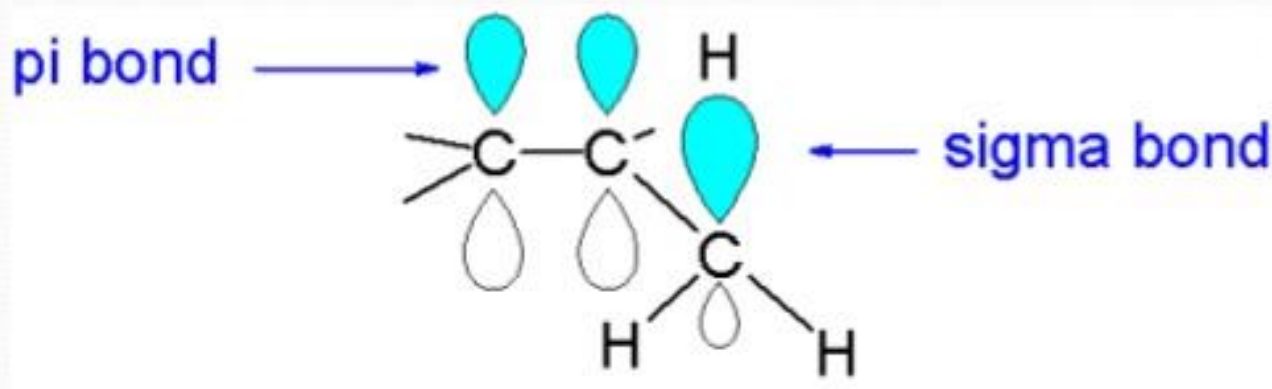


**cannot be resonance stabilised**

Very Reactive Radicals

# Hyper-conjugation

- Hyperconjugation is the interaction of the electrons in a sigma bond (usually C-H or C-C) with an adjacent empty or partially filled non-bonding p-orbital or antibonding  $\pi$  orbital or filled  $\pi$  orbital, to give an extended molecular orbital that increases the stability of the system.

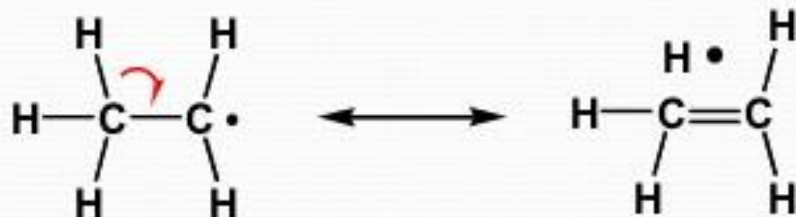


# Hyper-conjugation

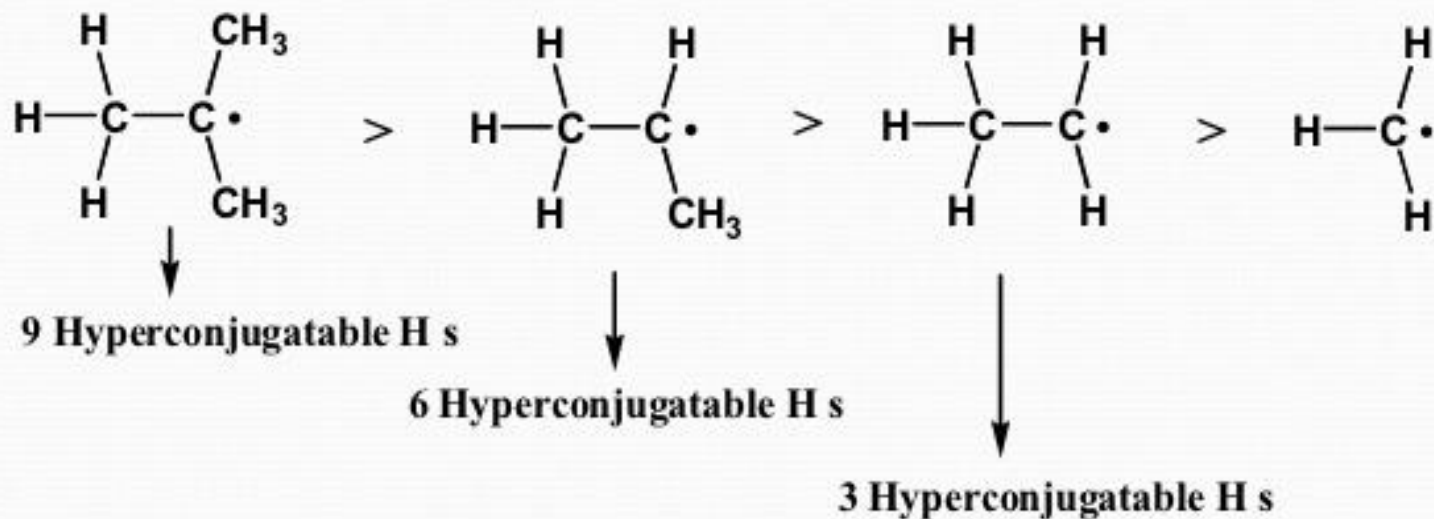
- Unstable charges on molecules are dispersed over the structure or due to presence of hydrogen attached to stabilize the molecule



### 3. Hyperconjugation



*thermodynamic stability*





## 4. Captodative effect

The captodative effect is the effect on the stability of a carbon-centred radical that is determined by the combined action of a captor (electron-withdrawing) and a dative (electron-donating) substituent, both attached to the radical centre



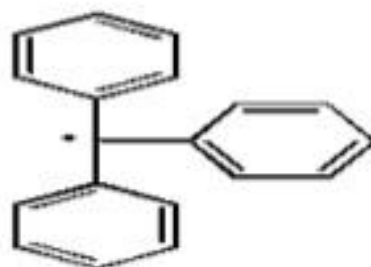
*c - Electron Withdrawing Group*

*d - Electron Donating Group*

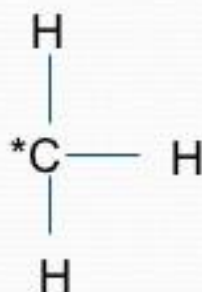
## b/ Kinetic Stability

This is generally due to **steric effects**

Steric effects arise from the fact that each atom within a molecule occupies a certain amount of space. If atoms are brought too close together, there is an associated cost in energy due to overlapping electron clouds, and this may affect the molecule's preferred shape and reactivity



Triphenyl methyl radical



Methyl radical is less stable as compared to triphenyl methyl radical

# REACTION OF FREE RADICALS

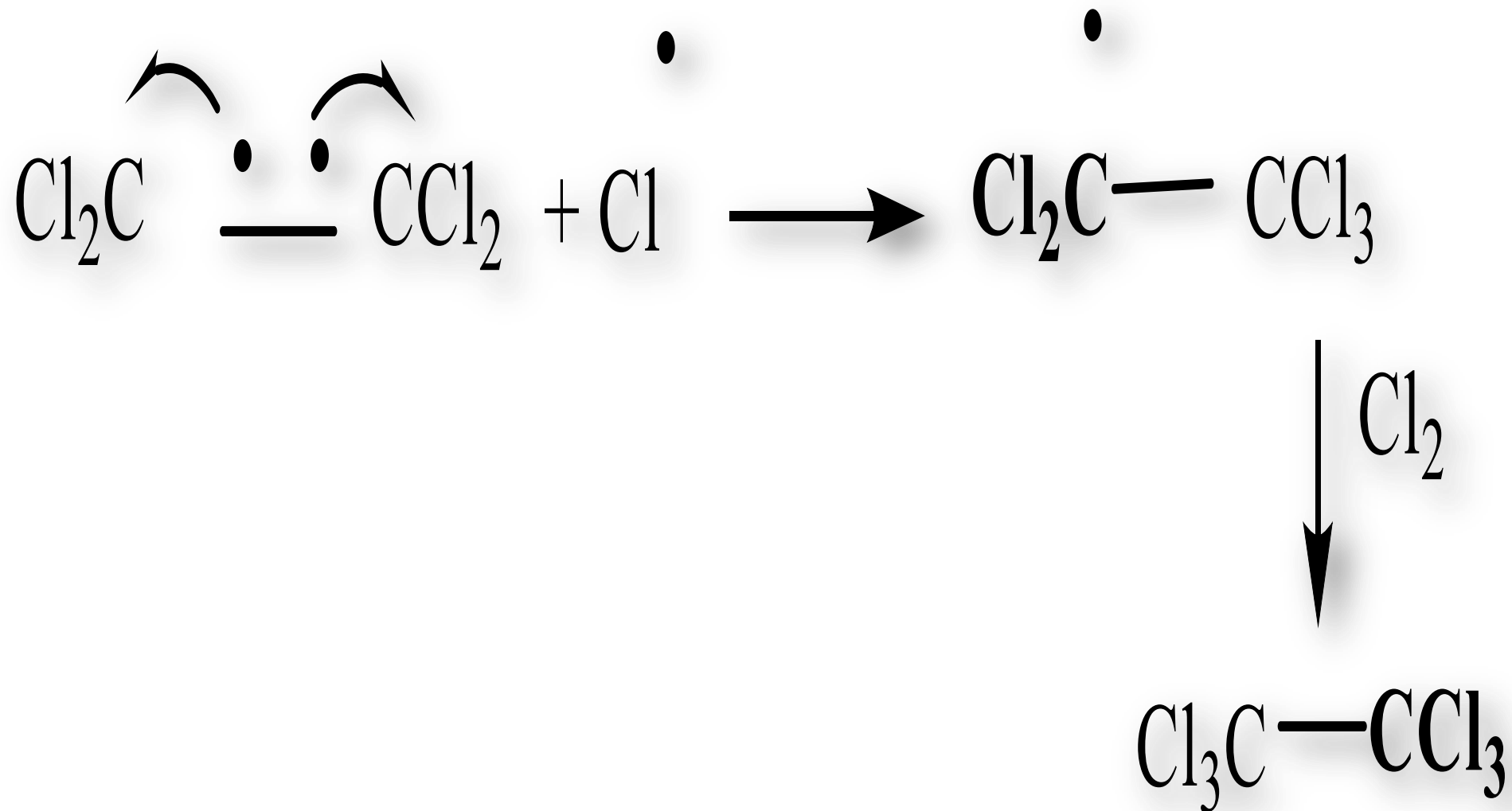
## THREE TYPE OF REACTION

**1- Addition**

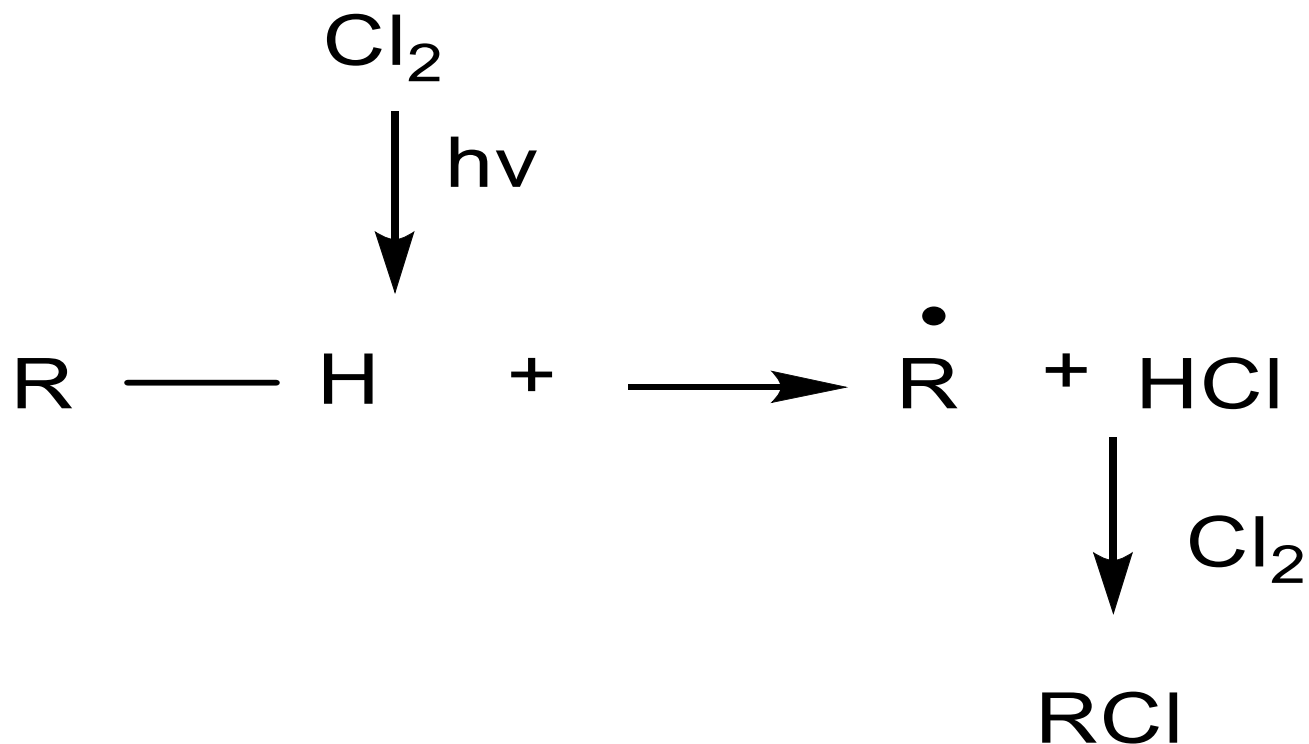
**2- Displacement**

**3- Rearrangement**

Addition

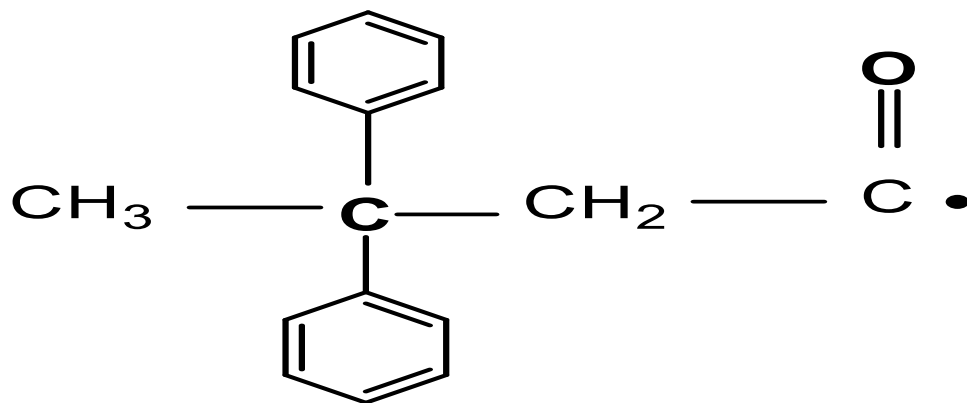


## 2- Displacement

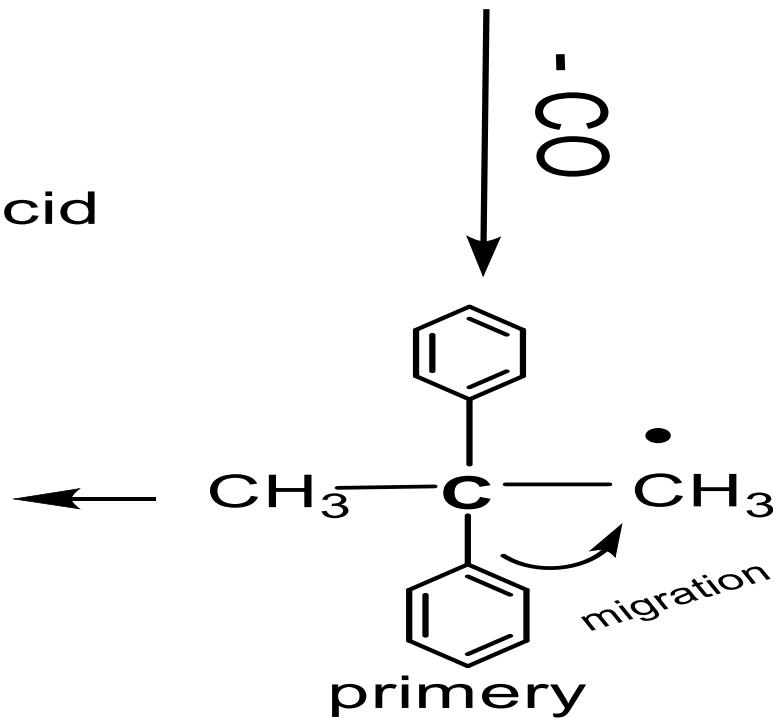
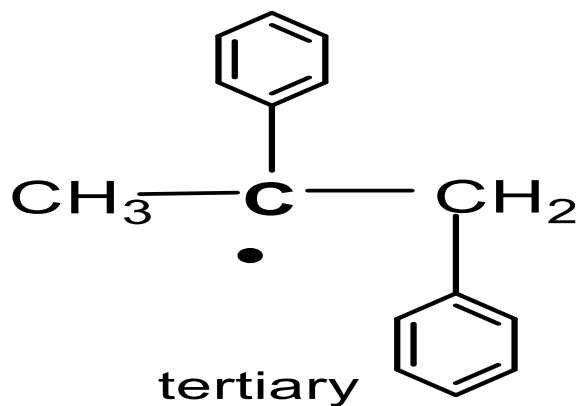




### 3- Rearrangement



3,3diphenylbutric acid



# References

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